The Influence of Cigarette Smoking on Lung Function in Patients with Idiopathic Pulmonary Fibrosis[1-3]

DAVID A. SCHWARTZ,[4] ROBERT K. MERCHANT,[5] RICHARD A. HELMERS, STEVEN R. GILBERT,[6] CHARLES S. DAYTON, and GARY W. HUNNINGHAKE

SUMMARY The purpose of this investigation was to quantify the effect of cigarette smoking on standard measures of lung function in patients with idiopathic pulmonary fibrosis (IPF). Our study population consisted of 73 patients in whom IPF had been clinically diagnosed; in 67% the diagnosis was confirmed by open lung biopsy. The average age was 63 yr; 62% were men, and 70% were either former or current cigarette smokers. Current cigarette smokers were found to have a greater percent predicted residual volume. Interestingly, in a univariate analysis, pack-years of cigarette smoking was found to be directly associated with increased measures of lung volumes (TLC, FRC, and RV) and diminished gas exchange (D_{LCO}). Linear multivariate regression models demonstrated that current cigarette smokers have greater measures of RV and FRC and that increasing pack-years of cigarette smoking is associated with diminished gas exchange. Importantly, the FEV_1/FVC ratio was not significantly related to either smoking status or pack-years of cigarette smoking. Results from our study indicated that among patients with IPF, current cigarette smokers will tend to trap air (higher RV and FRC), and that cigarette smoking appears to adversely alter gas exchange. Moreover, IPF appears to reduce the likelihood of developing physiologic correlates of airflow obstruction among cigarette smokers. However, this does not imply that IPF prevents the development of cigarette-induced lung disease. In fact, the association between cigarette smoking and both increased lung volumes and diminished gas exchange suggests the presence of both emphysema and interstitial fibrosis. In aggregate, these findings indicate that measures of lung function may be insensitive in estimating the extent of restrictive, as well as obstructive, lung function in patients with pulmonary fibrosis who smoke cigarettes. However, the D_{LCO} appears to provide a means of assessing the relative contribution of IPF and cigarette smoking to impaired lung function. These findings have clear implications for diagnostic criteria used to evaluate patients with IPF and should be considered when assessing the degree of lung impairment in these patients.

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Introduction

Patients with idiopathic pulmonary fibrosis (IPF) typically have restrictive lung function with reduced lung volumes and an abnormally low diffusing capacity (1, 2). Epidemiologic studies have found that 60 to 70% of the patients with IPF are either former or current smokers (3, 4). Thus, patients with IPF who are or have been cigarette smokers may have IPF with coexisting emphysema. Although IPF and emphysema will have opposing effects on lung volumes, measures of airflow, elastic recoil of the lung, and structural elements of the lung parenchyma, the combined presence of these two disease processes should markedly compromise the overall capacity or function of the pulmonary system. Given these concerns, the simultaneous occurrence of IPF and emphysema may present problems in assessing the degree of functional impairment.

The purpose of this investigation was to quantify the effect of cigarette smoking on standard measures of lung function in patients with IPF. *A priori*, we hypothesized that the opposing effects of cigarette smoke and IPF on elastic recoil would obscure the reduction in lung volumes that has been traditionally associated with IPF and would minimize physiologic correlates of airflow obstruction in cigarette smokers. In contrast, we postulated that measures of gas exchange would provide a means of assessing the relative contribution of IPF and cigarette smoking to impaired lung function. To evaluate these hypotheses, we analyzed the determinants of standard measures of lung function in 73 patients with IPF.

Methods

Patient Population

In total, 73 patients with IPF were included in this study. They were identified as part of an ongoing research effort to prospectively study patients with diffuse interstitial lung disease. Although these subjects were largely recruited from the state of Iowa, all bordering states in the midwest contributed subjects to this study. Unfortunately, we do not know whether our study subjects are representative of all patients with IPF from this region of the country. However, the demographic features of our study population (table 1) were similar to the demographic characteristics of other reported series of patients with IPF (3, 4). The diagnosis of IPF was based on standard criteria (3, 5), which included either evidence of interstitial lung disease on chest radiograph or restrictive lung function with an open lung biopsy demonstrating varying degrees of interstitial fibrosis and intra-alveolar inflammatory cells. Strict exclusionary criteria were established and consisted of no clinically relevant environmental or occupational exposure history, no clinical findings of hypersensitivity pneumonitis, left ventricular failure, or systemic disease, and no granulomata or vasculitis on the biopsy specimen. Furthermore, each biopsy specimen was cultured, and patients were included only if the cultures were negative for bacteria, mycobacteria, and fungi. Of 73 subjects with IPF, 49 (67%) had open lung biopsies, and the remaining 24, even though they did not have open lung biopsies, fulfilled all of the clinical criteria. Study subjects without open lung biopsies were required to have interstitial fibrosis on the chest radiograph and re-

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[1] From the Pulmonary Disease Division, Department of Internal Medicine, The University of Iowa, Iowa City, Iowa.

[2] Supported by SCOR Grant HL-37121 from the National Heart, Lung, and Blood Institute.

[3] Correspondence and requests for reprints should be addressed to David A. Schwartz, M.D., M.P.H., Pulmonary Disease Division, Department of Internal Medicine, The University of Iowa College of Medicine, Iowa City, IA 52242.

[4] Recipient of Clinical Investigator Award ES-00203 from the National Institute of Environmental Health Sciences.

[5] Recipient of Clinical Investigator Award ES-00196 from the National Institute of Environmental Health Sciences.

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TABLE 1

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF STUDY SUBJECTS (n = 73)*

Age, yr	63.0 ± 12.4 (24.5–82.6)
Race	
White	72 (98.6%)
Black	1 (1.4%)
Sex	
Male	45 (61.6%)
Female	28 (38.4%)
Smoking history	
Never	21 (28.8%)
Former	44 (60.3%)
Current	7 (9.6%)
Pack-years of cigarette smoking	26.7 ± 25.3 (0–100.0)

* Values are expressed as the mean ± standard deviation with the range shown in parentheses for continuous variables and as numbers with percentages in parentheses for categorical variables.

strictive lung function, and to fulfill all of our exclusionary criteria. All study subjects were required to have full pulmonary function tests performed at the University of Iowa.

Pulmonary Function Testing

The pulmonary function tests consisted of standard spirometry using the Medical Graphics 1070 system (Medical Graphics, St. Paul, MN) and lung volumes via body plethysmography using the Medical Graphics 1085 system. A single-breath diffusing capacity was measured using the Medical Graphics 1070 system. The measurements of lung function were performed using standard protocols, and the American Thoracic Society guidelines (6, 7) were used to determine acceptability. The predicted normal values used were those of Morris and coworkers (8) for spirometry, Goldman and Becklake (9) for lung volumes, and Van Ganse and colleagues (10) for the diffusing capacity.

Statistical Analysis

Univariate comparisons were made to determine whether demographic or clinical variables influenced the standard measures of lung function. Because our pulmonary function data proved to be normally distributed, we used parametric statistics to evaluate all of our comparisons. Student's *t* test and analysis of variance were used to evaluate the relationship between categorical variables and measures of pulmonary function, and simple regression coefficients were used to evaluate the relationship between continuous variables and pulmonary function (11).

We used a multivariate linear regression model (12) to identify the independent determinants of lung function in patients with IPF. A linear model was generated that incorporated all potential confounders and determined the relative strength of the relationship between measures of pulmonary function and both smoking status and pack-years of smoking. After a linear model was established, all possible interactions were tested in a stepwise manner to determine if significant improvements could be achieved by inclusion of any of the interactive terms.

Results

Our study population had a mean age of 63 yr, with more than 60% men and approximately 70% either former or current cigarette smokers (table 1). These characteristics are similar to those in other reported series of patients with IPF (3–5, 13–15). Only one study subject in our patient population was black. Standard measures of pulmonary function in our study population showed a mild reduction in lung volumes and a moderate to severe decrease in the D_{LCO} (table 2).

Current cigarette smokers were found to have a greater percent predicted residual volume than never smokers with IPF (table 2). Interestingly, in a univariate analysis (table 3), pack-years of cigarette smoking was found to be directly associated with higher lung volumes (TLC, RV, and FRC) and a lower D_{LCO}. Importantly, the FEV_1/FVC ratio was not significantly related to either smoking status or pack-years of cigarette smoking.

To evaluate whether other variables might alter the nature of the relationship between cigarette smoking and lung function, we determined the association between several clinical factors and measures of lung function in patients with IPF. These analyses demonstrate that male subjects have a lower percent predicted D_{LCO} than do female subjects (43.9 versus 52.3%; p = 0.03); subjects who had an open lung biopsy had lower percent predicted measures of FEV_1 (70.3 versus 86.0%; p = 0.001), FVC (62.6 versus 71.1%; p = 0.004), TLC (72.2 versus 82.9%; p = 0.02), RV (81.2 versus 97.4%; p = 0.03), and FRC (76.9 versus 90.6%; p = 0.02) than did those who had not had an open lung biopsy; and subjects treated with steroids or steroids plus cytoxan tended to have lower measures of FEV_1 (p = 0.003), FVC (p = 0.002), TLC (p = 0.009), and FRC (p = 0.03) than did those subjects who were not receiving immune-modulators.

To further examine the strength of the relationship between cigarette smoking and lung function while controlling for potential confounders (sex and intervention with either an open lung biopsy or immunosuppressive therapy), we developed linear multivariate regression models for all measures of lung function (%FEV_1, %FVC, FEV_1/FVC ratio, %TLC, %RV, %FRC, and %D_{LCO}). Our multivariate models, which identify cigarette smoking (either pack-years or smoking status) as potentially significant determinants of lung function, are presented in table 4. These multivariate analyses demonstrated that current cigarette smokers have greater measures of RV and FRC. Importantly, pack-years of cigarette smoking was inversely related to the D_{LCO} and was the only independent predictor of this measure of gas exchange. In contrast, measures of airflow obstruction (i.e., FEV_1/FVC ratio) were not related to either smoking status or pack-years of smoking. Although potential interac-

TABLE 3

REGRESSION COEFFICIENTS (WITH STANDARD ERRORS IN PARENTHESES) FOR THE RELATIONSHIP BETWEEN PACK-YEARS OF CIGARETTE SMOKING AND MEASURES OF PULMONARY FUNCTION*

	Pack-Years of Cigarette Smoking	p Value
FEV_1	0.14 (0.11)	0.20
FVC	0.14 (0.09)	0.11
FEV_1/FVC ratio	−0.001 (0.001)	0.11
TLC	0.20 (0.10)	0.06
RV	0.33 (0.18)	0.07
FRC	0.27 (0.12)	0.03
D_{LCO}	−0.15 (0.07)	0.04

* For FEV_1, FVC, TLC, RV, and D_{LCO}, these values represent the mean percent predicted. The FEV_1/FVC ratio is expressed as the mean of the absolute values.

TABLE 2

PULMONARY FUNCTION IN ALL SUBJECTS WITH IPF (n = 73) AND THE RELATIONSHIP BETWEEN CIGARETTE SMOKING STATUS AND MEASURES OF LUNG FUNCTION*

		Cigarette Smoking History			
Lung Function	All Subjects (*n* = 73)	Never (*n* = 21)	Former (*n* = 44)	Current (*n* = 7)	p Value†
FEV_1	75.9 ± 20.5	74.5 ± 17.4	78.1 ± 22.8	65.1 ± 11.1	0.29
FVC	65.6 ± 16.7	64.1 ± 15.1	66.5 ± 18.5	65.0 ± 11.3	0.87
FEV_1/FVC ratio	81.9 ± 9.7	83.6 ± 8.3	81.4 ± 10.6	78.0 ± 7.0	0.40
TLC	76.0 ± 19.7	73.0 ± 18.6	75.9 ± 20.6	83.9 ± 17.1	0.46
RV	87.0 ± 30.9	82.1 ± 30.4	84.3 ± 29.3	114.4 ± 31.9	0.04
FRC	81.8 ± 24.1	78.5 ± 25.0	80.5 ± 22.6	96.9 ± 29.1	0.20
D_{LCO}	47.2 ± 15.7	50.3 ± 13.3	45.3 ± 16.4	52.0 ± 16.7	0.35

* For FEV_1, FVC, TLC, RV, and D_{LCO}, these values represent the mean (± SD) percent predicted. The FEV_1/FVC ratio is expressed as the mean of the absolute values.

† The p values were calculated by computing the F statistic for the between-group analysis of variance.

TABLE 4

MULTIVARIATE LINEAR MODELS FOR RELATIONSHIP BETWEEN CIGARETTE SMOKING AND MEASURES OF LUNG FUNCTION FOR PATIENTS WITH IPF

	RV	FRC	D_{LCO}
	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)
Pack-years	–	–	−0.15 (0.07)*
Current smoker	34.5 (11.5)†	19.8 (9.3)*	–
Open lung biopsy	−22.0 (7.5)†	−17.6 (6.0)*	–
Model R^2	0.22	0.15	0.07

* $p \leq 0.05$.
† $p \leq 0.001$.

tions were explored, none of the interactive terms substantially altered the individual components of the models or the overall fit of the multivariate equations.

Discussion

Results from our study indicate that cigarette smoking will increase measures of lung volumes and diminish gas exchange among patients with IPF and that IPF tends to obscure the effect of cigarette smoking on physiologic measures of airflow. These findings have clear implications for diagnostic criteria used to evaluate patients with IPF and should be considered when assessing lung impairment in these patients.

Our findings indicate that cigarette smoking causes patients with IPF to trap air (increased RV and FRC). However, patients with IPF are usually found to have a high FEV_1/FVC ratio and a reduced RV. Because neither cigarette smoking nor IPF are likely to directly impair the respiratory muscles or decrease the compliance of the chest wall, the observed increase in RV among smokers with IPF appears to be caused by either a loss of elastic recoil of the lung parenchyma or premature closure of the airways (16). Although both of these possible explanations appear to be contrary to the physiology described for IPF, peribronchiolar inflammation and bronchiolitis with impaired airflow has been observed in patients with IPF (17). Thus, air trapping in smokers with IPF may be the result of a combination of active inflammation and chronic peribronchiolar fibrosis in the small airways caused by both IPF and cigarette smoke. Alternatively, smokers with IPF may have patchy areas of emphysema, which attenuate the physiologic effects of IPF on elastic recoil and subsequently result in higher measures of lung volumes. Regardless of the mechanism(s), our findings indicate that lung volumes may not adequately define the degree of functional impairment in patients with IPF who smoke cigarettes.

IPF appears to reduce the likelihood of developing physiologic evidence of airflow obstruction among cigarette smokers. In fact, in our population of patients with IPF, cigarette smoking was not significantly associated with measures of airflow obstruction. Although opposing effects on elastic recoil of the lung parenchyma may account for these findings, IPF has been shown to cause mild peribronchiolar fibrosis (17, 18), which may stiffen the small airways and prevent their premature closure. However, this finding does not imply that IPF prevents the development of cigarette-induced lung disease. In fact, the association between cigarette smoking and both increased lung volumes and diminished gas exchange suggests the presence of the both emphysema and interstitial fibrosis. The normal FEV_1/FVC ratio simply means that cigarette smoking and IPF appear to have opposite effects on airway function and, by implication, airway structure. Although the combination of emphysema and IPF may result in normal physiologic measures, the presence of both diseases may have profound effects on functional limitation.

One must recognize that selection bias may weaken the strength of our observations. First, those who smoke cigarettes may be physiologically more fit (at least initially) than those who stop smoking or those who never start smoking. Second, cigarette smokers with IPF may be more likely to be referred to our medical center than never smokers with IPF. Because the prevalence of cigarette smoking in our subjects with IPF is similar to other reported series (3, 4), we believe that this form of selection bias is less likely.

Despite these concerns, results from our study indicate that traditional measures of lung volumes may not be helpful in identifying the presence and extent of restrictive lung function in cigarette smokers with IPF. The lung volumes appear to be insensitive measures of restrictive lung function in this population. Moreover, physiologic measures of airflow obstruction may not be accurate indicators of airway disease in cigarette smokers with pulmonary fibrosis. These findings imply that the physiologic criteria for the diagnosis of pulmonary fibrosis and assessment of impairment of lung function need to be evaluated among cigarette smokers with IPF in a manner different from that among nonsmokers with IPF.

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